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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,086	10/30/2003	Ronald H.P. Brus	2578-6158US	9184

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 12/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,086	BRUS ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8, 9, 11, and 17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-24 are pending in the application. In the prior action, the Final Action mailed on August 23, 2005, claims 1-24 were pending, with claims 1-7, 10, and 12-16 under consideration and rejected; and claims 8, 9, 11, and 17-24 withdrawn as being drawn to a nonelected inventions. The Applicant submitted an After-Final Reply on October 24, 2005, accompanied by an IDS.

2. Claims 1-7, 10, and 12-16 are pending and under consideration.

3. In view of the new rejection presented below, prompted by a reference cited in the IDS accompanying Applicant's argument, the Finality of the prior action is withdrawn.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on October 24, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **(Prior Rejection- Withdrawn)** Claims 1-7, 10, and 12-16 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for methods for the identification of compounds with antiviral activity against any virus "other than an adenovirus." In view of the Applicant's arguments in traversal, which are found persuasive, the rejection is withdrawn.

7. **(New Rejection)** Claims 1-7, 10, and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining if a compound interferes with a virus's life cycle comprising the use of a cell transformed with an adenovirus type 5 E1 protein, does not reasonably provide enablement for methods involving the transformation of any cell with any adenoviral E1 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors considered most relevant are

the guidance or direction provided, the presence of working examples, the predictability of the art, and the breadth of the claims.

The present claims are drawn to methods of identifying anti-viral compounds through the use of cells transformed with nucleic acids encoding adenoviral E1 proteins. The claims read on methods involving the use of any cell transformed with any adenoviral E1 protein-encoding gene. It is further noted that the Applicant asserts that such transformation results in the cells gaining susceptibility to infection by viruses that would not normally infect the untransformed cell. See e.g., Remarks in October 2005 Response, page 3 of 6. Although this limitation is not specifically found in the claims, the use of such cells for the identification of anti-viral compounds for viruses that do not normally infect them is implicitly included from the language of (e.g.) claim 3 which limits claim 1 to embodiments wherein the virus is normally capable of infecting the cell.

In support of these claims, the Applicant relies on teachings in the application (and in the art) indicating that transformation of a particular embryonic retina cell resulted in an immortalized cell line susceptible to a wide variety of viruses. See e.g., App., pages 11, 19-26. All of the examples provided in the application are directed to a single transformed cell line- the PER.C6 cell line. It is further noted that the PER.C6 line is transformed specifically with a plasmid encoding both the E1A and E1B sequence of an adenovirus serotype 5. See e.g., WO 01/38362, page 3 (of record in the October 2003 IDS). Thus, the application discloses only a single type of cell transformed with a specific type of adenoviral E1 nucleic acid.

Further, while the application relates to the transformation of cells generally, it nowhere identifies other types of cells that would be susceptible to immortalization with an adenoviral

sequence. However, in the arguments presented in the October 2005 Remarks (page 4), the Applicant asserts that adenoviral proteins are not useful for the transformation of any host cell, relying on the teachings of Gallimore et al. (Anticancer Res 6:499-508- cited in the October 2005 IDS). Upon consideration of the reference, it is noted that the reference does teach that certain cells were not successfully transformed by adenoviral serotype 12 E1 genes. Further, the reference also teaches that "[s]ignficant differences, in terms of transformation frequency and the behaviour of the transformants, have been reported for the effects of E1 or E1A regions of Ad 5 and Ad 12..." Page 500, right column. The reference exemplifies this in its reference to the fact that HEK cells were successfully transformed by Ad 5 E1, but not by Ad 12. Page 500, left column. Further, the reference also teaches that in the co-transformation of cells with adenoviral E1 genes and ras, the phenotype of the resulting cells varied with the "serotype of the E1A." Thus, the reference teaches that not all cells are susceptible to transformation with any adenoviral E1 protein, and that different E1 genes from different adenoviral serotypes result in cells with different phenotypes. In particular, these teachings of variable phenotypes indicate the extended viral susceptibility phenotype of the PER.C6 cells would not necessarily be present in any cell transformed by any E1 gene.

Because the application provides limited guidance in the identification of cells that may be transformed using any particular adenoviral E1 sequence and provides only a single working example, and as the art indicates that there is unpredictability in the ability of any particular adenoviral protein to transform different cells or to achieve a particular phenotype in any particular cell, the application provides insufficient information to enable those in the art to use any cell transformed with any adenoviral E1 protein in the claimed methods. The Applicant has

not provided sufficient evidence to demonstrate that any cell transformed with such proteins would be (1) immortalized or (2) made susceptible to a wider range of viral infections such that any such transformed cell could be used in to identify compounds that interfere with any virus' life cycle. The claims are therefore rejected as exceeding the scope of inventions for which the application has presented an enabling disclosure.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. **(Prior Rejection- Maintained)** Claims 1-7, 10, 12, 13, and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Burk et al. (WO 91/15573- of record in the October 2003 IDS) in view of Hateboer et al. (WO 00/63403- of record in the October 2003 IDS). The Applicant has presented four arguments in traversal of the rejection. First, the Applicant asserts that "there is no teaching or suggestion in the references that would indicate that one can investigate viruses generally using cells that they are not known to normally infect." The Applicant's second argument is that the Examiner has not provided adequate motivation for the combination of Burk and Hateboer in view of the failure of Hateboer to teach that the cells described therein would be useful in the replication of viruses other than adenoviruses. The Applicant's third argument in traversal is based on evidence suggesting that adenoviral E1 genes would not be successful in the transformation of cells. Finally, the Applicant asserts that the

Burk reference provides a list of genes that can be used to immortalize cells without any specific guidance towards the use of adenoviral E1 genes.

The Applicant's first argument in traversal, regarding the failure of the references to suggest the investigation of viruses through the use of E1 transformed cells that the virus does not normally infect is not found persuasive for three reasons. First, while this argument may be persuasive with respect to the claims regarding the use of "an essentially intact virus" there is nothing that would prevent those in the art from investigating the effect of potential drugs on individual viral proteins or genes (i.e. elements of the virus sufficient for performing a phase in the viral life cycle) in such cells.

Second, the argument is not coextensive with the evidence presented by the Applicant. The Applicant has shown only a single example of an E1 transformed cell that is capable of infection by viruses that do not normally infect the untransformed cell. This is the PER.C6 cell, a retinal cell transformed specifically with the E1 protein from an Adenovirus type 5. Thus, while this function may be an unexpected result, it is not an unexpected result that the Applicant has shown to be common to any cell transformed with an E1 protein from any adenovirus.

Thirdly and finally, there is no requirement in the claims that the cell used in the claimed method is a cell that is not normally infected by the target virus. Thus, the Applicant is asserting a limitation that is not found in the claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This argument is therefore also not found persuasive.

As the combined teachings of Burk and Hateboer do not, as asserted by the Applicant, rely on a teaching that the transformed cell is capable of infection by any virus, and as the claims do not require the use of such cells, the Applicant's first argument in traversal is not found persuasive.

The Applicant's second argument in traversal is an assertion that the Examiner has provided insufficient motivation for the combination of the Burk and Hateboer references. Previously, the Applicant asserted that "the Hateboer reference does not teach the use of cells transformed with the adenoviral oncogene for the replication of other viruses." This argument was not found persuasive in the prior action on the basis that the Applicant had not provided any support for the statement. In the present After-Final response, the Applicant further asserts that "it is not the applicant's duty to show that the reference teach away from the proposed combination." This argument is not found persuasive because the present rejection is not reliant on the use of the specific cells described in Hateboer for the replication of other viruses. Rather, the present rejection is based on the teachings of Burk suggesting the use of transformed cells for such replication (identification of anti-viral compounds), including cells transformed with a viral oncogenic gene, and the teachings in Hateboer indicating that the oncogenic E1 genes of adenoviruses may be used to transform cells. What the Applicant had not established is that adenovirus E1 transformed cells could not be used in the methods of Burk. Thus, the silence of Hateboer with reference to this use of the cells was not found persuasive as the use at issue in the present claims was suggested by Burk. The teachings of Burk provide adequate motivation for the use of the E1 oncogene to transform cells as indicated by Hateboer. To overcome a rejection

based on such a proper motivation to combine, it is Applicant's burden to present some evidence or response to overcome the rejection.

The Applicant's third argument is related to the second in that the Applicant has now presented evidence that not every adenoviral E1 transformed cell would be satisfactory for use in the claimed methods. In particular, the Applicant states that the Gallimore reference indicates that attempts to transform hepatocytes with E1 functions have been unsuccessful. This argument is not found persuasive. This is because the teachings of the lack of success in transforming hepatocytes are not directed to adenoviral E1 genes in general, but is limited to those of the adenovirus 12. Gallimore, page 500, left column. However, there are no teachings in the reference to indicate that the E1 gene of adenovirus type 5 were equally unsuccessful. Rather, the reference specifically indicates that type 12 viral genes are not as effective in inducing transformation as type 5. See e.g., page 500, right column (esp., paragraph 2 of section 3., stating "AD 5 E1 transformed HER cells >20 fold more efficiently that did AD 12 E1."). On page 500, the reference teaches that the HEK cells which were not successfully transformed with Ad 12 E1 genes were previously shown to be successfully transformed by Ad 5 E1. The teachings of Gallimore do not teach that hepatocytes may not be transformed using any E1 protein. The limited scope of the negative teachings in Gallimore are highlighted by the success in Burk of the transformation of baboon hepatocytes with an E1A encoding plasmid (in combination with plasmids encoding cellular myc). Pages 38-40. Thus, while the teachings of Gallimore indicate that not every adenoviral E1 protein would be effective in the transformation of cells as suggested by Hateboer and required by Burk, the reference indicates that those of ordinary skill

in the art would have had a reasonable expectation of success in the use of Ad 5 E1. The additional success in the transformation of baboon cells in Burk would have added to that expectation of success. The Applicant's third argument in traversal is therefore also not found persuasive.

The Applicant's fourth argument in traversal is that the Burk reference fails to specifically teach or suggest the use of adenoviral E1 genes for the transformation of cells used in the disclosed methods. This argument is not found persuasive for two reasons. First, the reference specifically suggests the use of adenoviral E1 protein encoding nucleic acids for the transformation of cells, and teaches a successful example thereof. See, page 4 (lines 4-6), and pages 38-40 (teaching the transformation of baboon hepatocytes). Thus, the Applicant's arguments are not found persuasive as the reference teaches the successful transformation of hepatocytes.

With respect to the second reason that the argument is not found persuasive, it is noted that the Applicant asserts that the reference presents numerous alternatives that could be used, and nowhere specifically teaches or suggests the use of adenoviral E1 genes. It is first noted that this rejection is not based on Burk alone. The combination of Burk's suggestion to use viral oncogenes with the indications in Hateboer and Gallimore that adenoviral, and Ad 5 in particular, E1 genes would be so useful are sufficient to render obvious the alternative use of these genes for the transformation of cells as suggested by Burk. The fact that the Burk reference chose certain examples over others is not a teaching away from the use of the E1 proteins. See e.g., *In re Fulton*, 73 U.S.P.Q. 2d 1141, at 1146 (stating "[t]he prior art's mere disclosure of

more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." The fact that Burk chose to exemplify certain alternatives does render non-obvious the use of viral oncogenes in general, or the E1 genes in specific, for the transformation of cells. Furthermore, it is noted that the Burk reference does teach the immortalization of a cell line through transformation with an adenoviral E1 encoding nucleic acid. See, Example 5, page 38.

For these reasons, and for the reasons of record, the rejection is maintained.

10. **(Prior Rejection- Maintained)** Claims 1-7, 10, 12-14, and16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Burk and Hateboer as applied to claims 1-3, 5-7, 12, 13, and 16 above, and further in view of Lin et al. (J Virol Methods 88: 219-25). The Applicant traverses this rejection on the same basis as was indicated with respect to the rejection over Burk and Hateboer above. For the reasons indicated above, these arguments are not found persuasive, and the rejection is maintained.

11. **(Prior Rejection- Maintained)** Claims 1-7, and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burk and Hateboer as applied to claims 1-3, 5-7, 12, 13, and 16 above, and further in view of Halliday et al. (WO 99/51776- of record in the October 2003 IDS). The Applicant traverses this rejection on the same basis as was indicated with respect to the rejection over Burk and Hateboer above. For the reasons indicated above, these arguments are not found persuasive, and the rejection is maintained.

Conclusion

12. No claims are allowed.

13. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Scholl et al., U.S. 6,071,744. This reference teaches that HEK cells are susceptible to infection by HSV and suggests the use of such cells for the identification of anti-HSV compounds. It is further noted that the Gallimore reference indicates that HEK cells have been transformed with Ad 5 E1 genes. Thus, in combination with the suggestion of Burk for the use of immortalized cells in such methods, these references would render obvious the claimed method as directed to the elected embodiment wherein the virus is HSV. However, as the claims are not limited to HSV, the teachings of the Scholl reference does not add anything further to the previously cited references.

14. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on October 24, 2005 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

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